

Bayer CropScience

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201-16683



Mr. Stephen L. Johnson, Administrator
US Environmental Protection Agency
PO Box 1473
Merrifield, VA 22116
Attention: Chemical Right-to-Know Program

Submission of documents for 1-(4-chlorophenyl)-4,4-dimethyl-3-pentanone (CAS# 66346-01-8) under the HPV Challenge Program, AR-201, via electronic submission to oppt.ncic@epa.gov, chem.rtk@epa.gov, sheridan.diane@epamail.epa.gov, and townsend.mark@epamail.epa.gov

February 4, 2008

Dear Administrator,

Bayer CropScience
Institute Site
P. O. Box 1005
Institute, WV 25112
Tel. 304 767 6680
Fax 304 767 6294

Bayer CropScience LP (BCS) is submitting the final test plan and robust summaries on 1-(4-chlorophenyl)-4,4-dimethyl-3-pentanone. The test plan is being submitted electronically as a pdf file. The robust summaries are in the IUCLID format and are being submitted as an IUCLID export file as well as a pdf file. BCS believes that with this submission, all endpoints required under the HPV Challenge Program have been fulfilled.

If you have any questions regarding this submission, please contact Dr. Ann Blacker by phone (919-549-2973) or e-mail (ann.blacker@bayercropscience.com).

Sincerely,

John M. Wey
Head, HSE Expertise Center
Bayer CropScience
Tel 304-767-6680
mike.vey@bayercropscience.com

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**Bayer CropScience LP Response to EPA Comments on Chemical RTK HPV Challenge
Submission: 1-(4-Chlorophenyl)-4,4-dimethyl-3-pentanone**

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Summary of EPA Comments

The sponsor, Bayer CropScience LP, submitted a test plan and robust summaries to EPA for 1-(4-chlorophenyl)-4,4-dimethyl-3-pentanone (CAS No. 66346-01-8) dated December 29, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 25, 2004.

EPA has reviewed this submission and reached the following conclusions:

1. Physicochemical Properties. The melting point, vapor pressure, partition coefficient, and water solubility data are adequate for the purposes of the HPV Challenge Program. The submitter needs to check the accuracy of the boiling point value. Bayer CropScience (BCS) LP Response: Noted, see response below.
2. Environmental Fate. Data are adequate for the purposes of the HPV Challenge Program. Bayer CropScience LP Response: Noted.
3. Health Effects. The acute toxicity data are adequate, but the submitter needs to address deficiencies in the robust summaries. The submitter's proposal for reduced health testing based on a closed-system intermediate (CSI) claim was not adequately supported. Thus, there are data gaps for repeated-dose, genetic (chromosome aberrations), and reproductive/developmental toxicity. Bayer CropScience LP Response: Noted, see response below.
4. Ecological Effects. The acute fish and invertebrate toxicity data are adequate for the purposes of the HPV Challenge Program. The algal toxicity data are inadequate. EPA recommends that the submitter provide measured data on an analog or conduct testing on the sponsored chemical. Bayer CropScience LP Response: Noted, see response below.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the 1-(4-chlorophenyl)-4,4-dimethyl-3-pentanone Challenge Submission

General

The submitter included a separate, confidential business information (CBI) claim that the sponsored chemical was a closed-system intermediate. EPA reviewed this information and determined that the claim was not supported. Bayer CropScience LP Response: Noted.

Genetic Toxicity – Gene Mutations. The summary for a negative reverse mutation assay in *Salmonella typhimurium* is inadequate. The estimated Henry's Law constant of 1.51×10^{-2} atm-m³/mole (EPIWIN) suggests the potential for volatilization from the test vessels. The submitter did not state whether the study was conducted in a closed system with analytical monitoring of exposure concentrations. If the test was not conducted under these conditions, the submitter needs to provide other gene mutation data or conduct a new test. Bayer CropScience LP Response: Additional study details have been incorporated into the robust (IUCLID) summary for the Ames assay. With regard to EPA's concern about the volatility of the test material, BCS is not able to replicate the Henry's Law constant of 1.51×10^{-2} atm-m³/mole estimated by EPA using EPIWIN. Entering only the CAS number (66345-01-8) into EPIWIN version 3.12 provides a Henry's Law constant of 2.823×10^{-5} atm-m³/mole while inputting available experimental data (vapor pressure and water solubility) produces a Henry's Law constant of 7.07×10^{-6} atm-m³/mole (see attached EPIWIN outputs). Both of these values indicate low volatility. The vapor pressure of 0.00066 hPa (0.000495 mm Hg) at 20 °C further supports the low volatility of this chemical.

Regardless of EPA's concern about the volatility of the substance, the Ames assay performed with HWG alkylketone is valid for the following reasons:

- The chemical was determined to be stable in the vehicle (DMSO) demonstrating that the chemical was not volatilizing from the vehicle. The stability data have been added to the robust (IUCLID) summary.
- Evidence of bacteriotoxicity was observed as indicated by thinning of background lawn for all bacterial strains at 50 to 100 ug/plate and higher, a significant reduction in number of revertants per plate (> 50% decrease compared to vehicle control) at 1000 ug/plate and higher for strains T1535, 100, and 1537, and a significant reduction in bacterial titers for all strains at 100 to 400 ug/plate and higher. Thus, even if volatilization was occurring, sufficient test material was present in the culture media to produce a bacteriotoxic response.
- The Ames assay is a qualitative and not a quantitative test. Repeating the assay in a closed system might lower the level at which bacteriotoxicity is seen (assuming volatilization was present in the existing study) but is not likely to impact the conclusion of the study that HWG alkylketone is not mutagenic. As stated above, evidence of bacteriotoxicity with all strains indicates the presence of the test material in the culture media and thus exposure to the bacteria.

Thus, in summary, the existing Ames assay is valid based on analytical data demonstrating stability of HWG alkylketone in the vehicle and bacteriotoxicity evidencing test material to be present in the culture media. The Ames assay produces only a qualitative result, i.e. positive or negative, and the concentration or exposure at

which that result occurs is never taken into consideration in either the hazard or risk assessment.

Genetic Toxicity – Chromosomal Aberrations. If the chemical is to be tested in vitro, the submitter needs to use a closed system with no head space and analytically monitor the chemical concentrations. Bayer CropScience LP Response: An in vivo micronucleus test has been conducted to fulfill the chromosome aberration endpoint.

Ecotoxicity (fish, invertebrates, and algae)

Fish, Invertebrates. The acute fish and aquatic invertebrate data are adequate. Bayer CropScience LP Response: Noted.

Algae. Only ECOSAR data were provided. The sponsor needs to provide existing measured data on an analog or test the sponsored substance according to OECD TG 201. Bayer CropScience LP Response: Agree. An OECD TG 201 study has been conducted to fulfill the algae ecotoxicity endpoint.

Specific Comments on the Robust Summaries

Health Effects

Acute Toxicity. The submitter needs to report whether or not body weight determinations were made and to tabulate toxicity signs by dose level and sex. Bayer CropScience LP Response: Agree. Discussion of body weight determination and clinical signs by dose level and sex have been included in the study summaries.

Genetic Toxicity – Gene Mutations. The submitter needs to indicate the number of replicates per concentration, criteria for a positive response (i.e., define 'biologically relevant increase'), statistical method used, whether or not cytotoxicity was observed in the repeat study, concentrations tested in the repeat study (instead of a range), and the mean number of revertant colonies per plate for treated and control cultures. Bayer CropScience LP Response: Agree. The requested information has been added to the study summary.

Ecological Effects

Fish and Invertebrates. The submitter needs to identify the method used to measure the chemical in the fish and daphnia assays. Bayer CropScience LP Response: For the fish studies, the LC50-values given refer to measured values, because analytical control of the concentrations showed that with the exception of the highest concentration (10.0 mg active ingredient (a.i.)/l) the mean measured values were greater than 80 % of the nominal values in all aquaria. This information is included in the study summaries. For the daphnia study, the numbers quoted are nominal concentrations, since an analytical

check of the test concentrations is not included in the specified Guideline for this 48 hour acute test.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The melting point, vapor pressure, partition coefficient, and water solubility data are adequate for the purposes of the HPV Challenge Program. Bayer CropScience LP Response: Noted.

Boiling Point. The submitter provided a boiling point value of 178 °C at 0.046 hPa (0.0345 mm Hg). EPA used this value to estimate (via the NOMO5 program) a boiling point of 460 °C at 760 mm Hg. EPA considers this value to be too high. From the submitter's vapor pressure data at various temperatures, however, EPA calculated boiling point values of 303.9 °C, 299.4 °C, and 298.7 °C at 760 mm Hg, values that seem more reasonable. The submitter needs to check the accuracy of its submitted value and provide one at 760 mm Hg. Bayer CropScience LP Response: The boiling point value of 178 °C originally provided in the dossier does not agree with other internal documentation. A value of 270 °C is provided on the Bayer MSDS, is similar to the value of approximately 290 °C estimated using EPIWIN version 3.12, and is considered the critical value.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

Available data for these endpoints are adequate for the purposes of the HPV Challenge Program. Bayer CropScience LP Response: Noted.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

The acute toxicity data are adequate. Data are inadequate for repeated-dose toxicity, reproductive/ developmental toxicity, gene mutations, and chromosomal aberrations. EPA agrees with the submitter that testing is needed for chromosomal aberrations and developmental toxicity. EPA has determined that the submitter's Closed System Intermediate claim (submitted as CBI; analysis not shown here) was not adequately supported (the submitter needs to consult the Guidance for Testing Closed System Intermediates at <http://www.epa.gov/chemrtk/guidocs.htm>). Thus EPA recommends that the submitter conduct testing according to OECD TG 422 to address the repeated-dose and reproductive/developmental toxicity endpoints. Bayer CropScience LP Response: 1. Agree the acute toxicity data are adequate. 2. An OECD TG 422 has been conducted to provide data for the repeated dose, reproductive/developmental toxicity endpoints. 3. An in vivo micronucleus test has been conducted to fulfill the chromosome aberration endpoint. Disagree that the bacterial gene mutation assay is inadequate (see below). 4. Agree to withdraw the closed system intermediate claim.

Appendix: Epiwin Output

EPIWIN version 3.12 output based on CAS number only entry

SMILES : O=C(C(C)(C)C)CCc1ccc(cc1)CL
CHEM : 3-Pentanone, 1-(4-chlorophenyl)-4,4-dimethyl-
CAS NUM: 066346-01-8
MOL FOR: C13 H17 Cl1 O1
MOL WT : 224.73

----- EPI SUMMARY (v3.12) -----

Physical Property Inputs:

Water Solubility (mg/L): -----
Vapor Pressure (mm Hg) : -----
Henry LC (atm-m3/mole) : -----
Log Kow (octanol-water): -----
Boiling Point (deg C) : -----
Melting Point (deg C) : -----

Log Octanol-Water Partition Coef (SRC):

Log Kow (KOWWIN v1.67 estimate) = 3.97

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPWIN v1.41):

Boiling Pt (deg C): 289.88 (Adapted Stein & Brown method)
Melting Pt (deg C): 69.96 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 0.00126 (Modified Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.41):

Water Solubility at 25 deg C (mg/L): 13.2
log Kow used: 3.97 (estimated)
no-melting pt equation used

Water Sol Estimate from Fragments:

Wat Sol (v1.01 est) = 13.526 mg/L

ECOSAR Class Program (ECOSAR v0.99h):

Class(es) found:
Neutral Organics

Henrys Law Constant (25 deg C) [HENRYWIN v3.10]:

Bond Method : 9.21E-006 atm-m3/mole
Group Method: Incomplete

Henrys LC [VP/WSol estimate using EPI values]: 2.823E-005 atm-m3/mole

Probability of Rapid Biodegradation (BIOWIN v4.02):

Biowin1 (Linear Model) : 0.3357
Biowin2 (Non-Linear Model) : 0.0219

Expert Survey Biodegradation Results:

Biowin3 (Ultimate Survey Model): 2.1865 (months)
Biowin4 (Primary Survey Model) : 3.1140 (weeks)

Readily Biodegradable Probability (MITI Model):

Biowin5 (MITI Linear Model) : 0.2629
Biowin6 (MITI Non-Linear Model): 0.1086

Ready Biodegradability Prediction: NO

Atmospheric Oxidation (25 deg C) [AopWin v1.91]:

Hydroxyl Radicals Reaction:

OVERALL OH Rate Constant = 7.7665 E-12 cm³/molecule-sec

Half-Life = 1.377 Days (12-hr day; 1.5E6 OH/cm³)

Half-Life = 16.526 Hrs

Ozone Reaction:

No Ozone Reaction Estimation

Soil Adsorption Coefficient (PCKOCWIN v1.66):

Koc : 1099

Log Koc: 3.041

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v1.67]:

Rate constants can NOT be estimated for this structure!

BCF Estimate from Log Kow (BCFWIN v2.15):

Log BCF = 2.357 (BCF = 227.7)

log Kow used: 3.97 (estimated)

Volatilization from Water:

Henry LC: 9.21E-006 atm-m³/mole (estimated by Bond SAR Method)

Half-Life from Model River: 96.83 hours (4.034 days)

Half-Life from Model Lake : 1182 hours (49.25 days)

Removal In Wastewater Treatment:

Total removal: 29.02 percent

Total biodegradation: 0.31 percent

Total sludge adsorption: 28.35 percent

Total to Air: 0.37 percent

(using 10000 hr Bio P,A,S)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.67	33	1000
Water	12.9	1.44e+003	1000
Soil	82.8	2.88e+003	1000
Sediment	3.61	1.3e+004	0

Persistence Time: 1.66e+003 hr

EPIWIN version 3.12 output based on entries of CAS number, water solubility, and vapor pressure

SMILES : O=C(C(C)(C)C)CCc1ccc(cc1)CL

CHEM : 3-Pentanone, 1-(4-chlorophenyl)-4,4-dimethyl-

CAS NUM: 066346-01-8

MOL FOR: C13 H17 CL1 O1

MOL WT : 224.73

----- EPI SUMMARY (v3.12) -----

Physical Property Inputs:

Water Solubility (mg/L): 20.7

Vapor Pressure (mm Hg) : 0.000495

Henry LC (atm-m³/mole) : -----

Log Kow (octanol-water): -----
Boiling Point (deg C) : -----
Melting Point (deg C) : -----

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.67 estimate) = 3.97

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPWIN v1.41):
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ECOSAR Class Program (ECOSAR v0.99h):
Class(es) found:
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Henrys Law Constant (25 deg C) [HENRYWIN v3.10]:
Bond Method : 9.21E-006 atm-m3/mole
Group Method: Incomplete
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Probability of Rapid Biodegradation (BIOWIN v4.02):
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Rate constants can NOT be estimated for this structure!

BCF Estimate from Log Kow (BCFWIN v2.15):
Log BCF = 2.357 (BCF = 227.7)

log Kow used: 3.97 (estimated)

Volatilization from Water:

Henry LC: 7.07E-006 atm-m3/mole (calculated from VP/WS)
Half-Life from Model River: 125.7 hours (5.236 days)
Half-Life from Model Lake : 1496 hours (62.35 days)

Removal In Wastewater Treatment:

Total removal: 28.95 percent
Total biodegradation: 0.31 percent
Total sludge adsorption: 28.36 percent
Total to Air: 0.28 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.655	33	1000
Water	13	1.44e+003	1000
Soil	82.7	2.88e+003	1000
Sediment	3.64	1.3e+004	0

Persistence Time: 1.67e+003 hr
